3. RESPONSE/REMARKS

3.1 STATUS OF THE CLAIMS

Claims 1, 10-14, 16, 17, 19, 20, 24 and 32-47 were pending at the time of the action.

Claims 2-9, 12, 15, 16, 18, 21-23, 25-31 and 43-45 have been canceled without prejudice or disclaimer.

Claims 33-42 have been withdrawn from consideration on the merits.

Claims 1, 10, 19, 20, 24, 32, 46 and 47 have been amended herein.

Claims 1, 10, 11, 13, 14, 17, 19, 20, 24, 32-42 and 46-47 are now pending in the case.

3.2 SUPPORT FOR THE CLAIMS

Support for the pending claims can be found throughout the original specification, claims, and figures as filed. It is Applicants' belief that no new matter is included by entry of the present amendment.

3.3 THE OBJECTION TO THE SPECIFICATION HAS BEEN OVERCOME.

Page 27, line 3 of the Specification has been amended as requested by the examiner to identify the amino acid sequence VKGQ corresponding to amino acids residues 47 to 50 in SEQ ID NO:4.

Applicants respectfully request that the objection now be withdrawn.

3.4 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 102(A) MAY BE OVERCOME BY A SUBMISSION IN ACCORDANCE WITH 37 C. F. R. § 1.131.

The Action at page 3 rejects claims allegedly as being anticipated under 35 U. S. C. § 102(a) by Yamano* et al. (J. Gene Med., *3:450-547, August 2, 2001; hereinafter "Yamano").

Applicants respectfully traverse.

Without acquiescing in any way to the propriety of the rejection, and without agreeing in any manner with the Office's characterization of what Yamano does or does not "teach", or whether or not any aspects of the present invention is potentially "anticipated" by the reference, Applicants respectfully note for the record that the cited reference was published in August 2001, less than a year before the April 19, 2002 priority date claimed by the present application, and as such, may elect to remove Yamano as prior art pursuant to a submission on 37 C.F.R. § 1.131.

Applicants provide constructive notice of their intent to file a Statutory Declaration of the named inventors to antedate the reference by evidencing Applicants' invention of the claimed subject matter in the United States prior to the August 2, 2001 publication of Yamano.

The Statutory Declaration is being submitted to the Office under separate cover and provides documentary evidence that the inventors conceived of the claimed invention in the United States at a time prior to the August 2, 2001 publication of Yamano; (b) that the inventors acted diligently in both the conception and reduction to practice of the invention in the United States from a time prior to the August 2, 2001 publication of Yamano; (c) that the Assignee of Record and its patent counsel acted diligently to prepare and file a provisional patent application for the invention; (d) that the Assignee of Record and its patent counsel further acted diligently to convert the provisional application to a PCT international application and subsequently

nationalize the PCT international application in the United States giving rise to the present 371 national stage application; and e) that subsequent to a time prior to the August 2, 2001 publication of Yamano, the inventors have diligently continued in their research efforts involving various embodiments of the invention as described in the present, and in the prior provisional patent application, from which the present application properly ultimately claims priority.

3.5 THE FIRST REJECTION OF CLAIMS UNDER 35 USC § 102(B) IS OVERCOME.

The Action at page 3 also rejected claims allegedly as being anticipated under 35 U. S. C. § 102(b) by Cottard* et al. (Gene Ther., *73:1930-1939, 2000; hereinafter "Cottard").

Applicants respectfully traverse.

It is well established that a rejection on the grounds of anticipation requires the disclosure, in a single reference, of every element of a claimed invention and requires that each and every facet of the claimed invention be identified in the applied reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed. Cir. 1987); *Ex parte Levy*, 17 USPQ2d 1461 (B.P.A.I. 1990).

The Action notes that Cottard discloses an AAV vector comprising a CMV promoter/enhancer that encodes a human IL-4 protein in vitro using human 293 cells.

Applicants respectfully note that the pending claims are directed to an adeno-associated viral vector comprising a polynucleotide that expresses in *human pancreatic islet cells*, a biologically-active **IL-10** or **IL-10(I87A)** protein, not the IL-4 peptide disclosed in Cottard. Moreover, Cottard does not teach or suggest expression of these proteins in pancreatic islet cells,

thus another limitation of the pending claims is not taught in the reference. To that end, Applicants believe that the rejection should now be withdrawn.

3.6 THE SECOND REJECTION OF CLAIMS UNDER 35 U. S. C. § 102(B) IS OVERCOME.

The Action at page 4 also rejected claims allegedly as being anticipated under 35 U. S. C. § 102(b) by Flotte* et al. *(PCT Intl. Appl. Publ. No. WO 99/55564; hereinafter "Flotte").

Applicants respectfully traverse.

As noted above, for a claim to be rejected under this section of the statute, the cited reference must teach each and every element of the claimed invention. The Action notes that Flotte discloses AAV vectors and virions and isolated mammalian cells comprising such vectors, as well as the use of various promoters, enhancers, and polyadenylation signals to express various polypeptides in different types of cells, and also provides methods for treating different types of disease using various rAAV constructs.

Applicants again note, however, that the pending claims are directed to particular adeno-associated viral vectors comprising a polynucleotide that expresses in *human pancreatic islet cells*, a biologically-active **IL-10** or **IL-10(I87A)** protein. Flotte *et al* does not teach the specific rAAV vectors encoding an IL-10 or an IL-10(I87A) protein as claimed for the treatment of diabetes, and/or for expressing therapeutic levels of one of these proteins in human pancreatic islets cells. Therefore, Flotte *et al.* does not teach each and every element of the claimed invention; as such, Applicants respectfully believe that the rejection should be withdrawn.

3.7 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 102(E) MAY BE OVERCOME BY A SUBMISSION UNDER 37 C. F. R. § 1.132.

The Action at page 4 also rejected claims allegedly as being anticipated under 35 U. S. C. § 102(e) by Loiler* et al. *(U.S. Patent Appl. Publ. No. 2006/0292117; hereinafter "Loiler").

Applicants respectfully traverse.

Without acquiescing in any way to the propriety of the rejection, and without agreeing in any manner with the Office's characterization of what the published patent application by Loiler *et al* does or does not "teach", or whether or not any aspects of the present invention is potentially "anticipated" by the reference, Applicants respectfully note for the record that the cited application is commonly owned by the assignee of the present application, has at least one inventor in common, and as such, Applicants may elect to remove Loiler as prior art pursuant to M. P. E. P §§ 715.01(a), 715.01(c) and 716.10, and an *In re Katz*-styled submission in accordance with 37 C.F.R. § 1.132. To that end, Applicants provide constructive notice of their intent to file a Statutory Declaration under separate cover to remove the cited co-owned patent application as prior art.

3.8 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 102(E) IS OVERCOME.

The Action at page 5 rejected claims allegedly as being anticipated under 35 U. S.C. § 102(e) by Hildinger* et al. *(U. S. Patent 7,056,502; hereinafter "Hildinger").

Applicants respectfully traverse.

As noted above, for a claim to be rejected under this section of the statute, the cited reference must teach each and every element of a claimed invention. *Verdegaal Bros. v. Union*

Oil Co. of California, 2 USPQ2d 1051 (Fed. Cir. 1987); *Ex parte Levy*, 17 USPQ2d 1461 (B.P.A.I. 1990), *supra*.

The Action notes that Hildinger discloses AAV vectors and virions and isolated mammalian cells comprising such vectors, as well as the use of various promoters (*e.g.*, CMV promoter) and a "laundry list" of various potentially "useful" transgene products.

Applicants respectfully note, however, that the pending claims are directed to adeno-associated viral vectors comprising a polynucleotide that expresses in *human pancreatic islet cells*, a biologically-active IL-10 or IL-10(I87A) protein. Applicants do not find any teaching within Hildinger that provides rAAV vectors encoding an IL-10 or an IL-10(I87A) protein designed for expression in mammalian pancreatic islets in general, or in human pancreatic islet cells in specific. Thus, Hildinger does not teach each and every element of the claimed invention. Therefore, Applicants believe that the rejection should now be withdrawn.

3.9 THE REJECTION OF CLAIM 10 UNDER 35 U. S. C. § 103(A) IS OVERCOME.

The Action at page 7 rejected claim 10 allegedly as being obvious under 35 U. S. C. § 103(a) over Hildinger when taken with Xiao* et al. *(U. S. Patent 6,329,181; hereinafter, "Xiao").

Applicants respectfully traverse.

The Action states that Xiao describes "AAV vectors generally, and particular methods of making them." The Office considers that the combination of these two references makes claim 10 obvious, since Hildinger teaches the use of a human β-actin promoter in certain aspects, and Xiao states that the human β-actin promoter was a suitable promoter for use in an AAV vector."

Applicants respectfully traverse, and note for the record that a finding of obviousness under 35 U. S. C. § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. John Deere Co.*, 148 USPQ 459 (U.S. S.Ct. 1966).

The relevant inquiry is whether the prior art suggests the invention and whether the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 7 USPQ 2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success *must be found in the prior art* and not in the Applicant's disclosure (emphasis added) *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Thus, for the cited combination of references to render the present claims legally obvious under 35 U. S. C. § 103, the references must suggest the particular claimed recombinant AAV vectors, AAV virions, as well as transformed host cells, pluralities of viral particles, and kits that comprise one or more of the disclosed vectors and/or virions. Moreover, the combination must provide one of ordinary skill in the art with a reasonable expectation of obtaining such compositions, vectors, host cells, and kits.

The combination of cited references, alone or in combination with one or both of the secondary references characterized by the Action, cannot obviate the claimed invention when the references fail to provide the required suggestion or reasonable expectation of success of generating the disclosed AAV vectors, virions, and compositions and/or host cells comprising them.

Neither of the cited references provides a suggestion, reason, or the motivation to combine its teaching for the preparation of rAAV-based IL-10 or IL-10(I87A)-expressing DNA

constructs that are operably linked to a CMV enhancer sequence and that are also operably linked to a chicken β-actin promoter sequence. The present inventors have shown that these compositions and viral constructs are useful in methods for the *sustained expression* of *therapeutic levels* of interleukin polypeptide in the host cells (and pancreatic islet cells in particular) of a mammal, and these surprising and unexpected findings have been shown to be useful, novel, and non-obvious. The present specification teaches that the claimed vectors, compositions, virions, and host cells may be useful in not only the *treatment* of Type II diabetes, but also in the *prevention* of Type II diabetes as demonstrated in an acceptable animal model (*e.g.*, the murine *NOD* model of diabetes).

Because the claims in the case particularly point out the distinct features of the inventive methods disclosed in the Specification, and because each of such claims is clearly distinguished over the previously cited art (either alone or in combination) Applicants further believe that, as a matter of law, the rejection advanced under 35 U. S. C. § 103 cannot stand.

Applicants also urge the application of the standard held in the case of *In re Vaeck*, 20 U.S.P.Q. 1438 (Fed. Cir. 1991), in which the Federal Circuit stated that in order for an examiner to make out a *prima facie* case of obviousness two things must be shown:

(1) That the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention; and

(2) That the prior art must demonstrate a reasonable expectation of success of the invention.

Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the Applicant's disclosure (emphasis added).

Furthermore, in the case of *In re* Dow Chemical Co. (837 F. 2d 469, 5, U.S.P.Q.2d 1529, Fed. Cir. 1988) the court held that an "obvious-to-experiment" standard is not an acceptable

alternative for obviousness, and that there must be a reason or suggestion in the art, *other than* the knowledge learned from the Applicants' disclosure.

In the instant case, however, there is neither the suggestion nor the reasonable expectation of success. Even if one *could* somehow postulate that one or more of the cited references might suggest that the claimed rAAV viral vectors, viral particles, virions, or compositions similar to those disclosed in the application might, in an abstract sense, be *plausible*, there is certainly *no* teaching or suggestion as to how one would go about developing the specific viral constructs of the present invention, nor is there any suggestion in the cited references, either alone or in combination, that such an approach would be successful in treating and/or preventing any disease. The references relied upon by the Examiner, either alone or in combination, do not provide the motivation or the teaching for preparing the particular disclosed AAV vector-based polynucleotide compositions that comprise a nucleotide sequence encoding an IL-10 or an IL-10 I87A polypeptide operably linked to a CMV enhancer and a chicken β-actin promoter sequence. Likewise there is no motivation or teaching that such compositions, viruses, or transformed cells expressing such constructs would be useful to achieve sustained expression of therapeutically-effective serum levels of interleukin proteins when provided to an animal (or when expressed in pancreatic islet cells of such a mammal), nor is there a suggestion or an expectation that such compositions could be utilized in the methods disclosed for the treatment, prevention, and/or amelioration of symptoms of Type II diabetes in an animal, and in particular, in mammals such as humans.

Furthermore, the Applicant submits that *the combination of references relied upon by the Examiner also clearly fails to satisfy the tripartite test of* In re O'Farrell (7 U.S.P.Q.2d 1673,

1680, Fed. Cir. 1988). In *O'Farrell*, the Court held that in order for a reference or references to obviate an invention, it must be shown that the reference(s) contains:

(1) Detailed enabling methodology for practicing the claimed invention;

(2) A suggestion for modifying the prior art to practice the claimed invention; and

(3) Evidence suggesting that the invention would be successful.

In the present case (1) none of these references provides any teaching relevant to the question of how one of skill would proceed to prepare the claimed rAAV viral vector-based polynucleotide compositions, and most certainly does not provide any "detailed enabling methodology" for practicing the claimed invention; (2) none of the cited references in the present case provides any suggestion for combining the teachings of the individual references or for modifying either or both of these prior disclosures in a manner that would allow one to arrive at the surprising and unexpected findings disclosed in the present invention; and (3) none of the references provides evidence that the present invention would be successful in its use in the therapy or prophylaxis of diabetes in a mammal. Clearly the rejection is improper as it fails the tripartite test of *In re O'Farrell.*

Applicant asserts that any combination of the cited references is, at best, merely an invitation for further experimentation in the field, and at most, an "obvious-to-try" situation. However, there is *no* reasonable expectation of success, *nor* is there the motivation or teaching to guide a skilled artisan how to achieve such success. The Federal Circuit, in the case of *In re Geiger* (815 F.2d. 686, 2 U.S.P.Q.2d 1276, Fed. Cir. 1987), held that obviousness cannot be established by combining the teachings of the prior art to produce a claimed invention, absent some teaching, suggestion or incentive supporting the combination. Again, Applicant believes that the rejection fails the test of *In re Geiger.*

Further, in *Amgen v. Chugai Pharmaceutical Co. Ltd.*, (927 F. 2d 1200, 18 U.S.P.Q. 2d 1016, 1022, Fed. Cir. 1991) the Court affirmed that obviousness under 35 U. S. C. § 103 is a question of law, and that both the suggestion and the expectation of success must be found in the prior art, and not in the Applicant's disclosure. Because the suggestion and expectation of success are absent in the cited art, Applicant asserts that the rejection also fails the test of *Amgen v. Chugai Pharmaceutical Co. Ltd.*

Turning to the specific rejections, pending claim 10 is drawn to rAAV vectors that comprise a specific chicken β-actin promoter, and not the human sequence, which is inherently non-identical to the chicken sequence. Applicants assert that the generic discussion of "known" promoters at the time of the instant filing would not have been sufficient to cause one of skill in the art to select the particular sequence claimed in claim 10. As such, Applicants respectfully request that the rejection of claim 10 now be withdrawn.

For these reasons, Applicants respectfully request that this obviousness rejection be withdrawn because it fails to meet the requirements for legal obviousness under 35 U.S.C. 103(a).

3.10 THE REJECTION OF CLAIMS 46 AND 47 UNDER 35 U. S. C. § 103(A) IS OVERCOME.

The Action at page 7 further rejects claims 46 and 47 allegedly as being obvious under 35 U. S. C. § 103(a) over Hildinger when taken with Xiao, and further in view of PIR Acc No. A25946 or PIR Acc. No. A38580. The Office considers that it would have been obvious to utilize rAAV vectors comprising polynucleotides that encode human IL-10 and IL-4 sequences, because those sequences "were known in the prior art."

Applicants respectfully traverse, and note for the record that pending claims 46 and 47 are drawn to adeno-associated viral vectors comprising at least a first polynucleotide that comprises a chicken β-actin promoter operably positioned upstream of an isolated nucleic acid segment that encodes a biologically-active human interleukin polypeptide comprising either the sequence of SEQ ID NO:1 (the human IL-10 protein sequence) or, alternatively, the sequence of SEQ ID NO:2, in which the isoleucine at amino acid 87 is replaced by an alanine (I87A).

3.11 REQUEST FOR EXAMINER INTERVIEW

Pursuant to M. P. E. P. § 713.01 and 37 C. F. R. § 1.133, Applicants hereby request an interview between the Examiner and their undersigned representative in order to facilitate an expeditious conclusion of prosecution on the merits in the present application, and to permit expedited allowance and issuance of the pending claims prior to the issuance of any subsequent action on the merits.

Should any issues remain in the mind of the Examiner, or should any claims remain rejected for any reason following entry of the present amendment and consideration of the remarks and response herein, Applicants respectfully request that pursuant to M. P. E. P. §§ 408 and 713.09, the Examiner contact the undersigned representative to arrange a telephonic

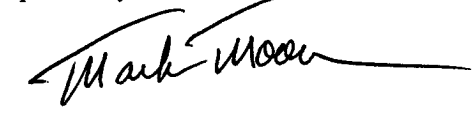
Examiner Interview at a mutually convenient time to discuss favorable disposition of the case and the resolution of any remaining issues of record ***before the issuance of any subsequent Action on the Merits***. Applicants appreciate in advance the Examiner's willingness to arrange such an interview, should any issues concerning patentability of the pending claims remain following entry of the present amendment and consideration of the Amendment and Response submitted herewith.

3.12 CONCLUSION

It is respectfully submitted that all claims are fully enabled by the Specification, and that all claims are definite and free of the prior art. Applicants believe that the claims are acceptable under all sections of the Statutes and are now in condition for ready allowance, and that all of the concerns of the Examiner have been resolved. Applicants earnestly solicit concurrence by the Examiner and the issuance of a Notice of Allowance in the case with all due speed. Applicants note for the record their explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim from the present and parent cases.

Should the Examiner have any questions, a telephone call to the undersigned Applicants' representative would be appreciated, particularly in advance of any subsequent action on the merits.

Respectfully submitted,



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I hereby certify that this correspondence is being filed with the U.S. Patent and Trademark Office *via* EFS-Web on October 29, 2007.

Susan Imhoff